

## Critical roles of a small conductance $\text{Ca}^{2+}$ -activated $\text{K}^{+}$ channel (SK3) in the repolarization process of atrial myocytes.

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### Public Summary:

Small conductance calcium-activated potassium (SK) channels are found to preferentially in the human heart muscle cells in the atrial chamber. These channels play an important role in the return of electrical impulses associated with heartbeats to the resting baseline. In particular, presence of SK3, a member of the SK channels, can significantly accelerate the observed return to baseline.

### Scientific Abstract:

**AIMS:** Small conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$  channels (KCa2 or SK channels) have been reported in excitable cells, where they aid in integrating changes in intracellular  $\text{Ca}^{2+}$  ( ) with membrane potentials. We have recently reported the functional expression of SK channels in human and mouse cardiac myocytes. Additionally, we have found that the channel is highly expressed in atria compared with the ventricular myocytes. We demonstrated that human cardiac myocytes expressed all three members of SK channels (SK1, 2, and 3); moreover, the different members are capable of forming heteromultimers. Here, we directly tested the contribution of SK3 to the overall repolarization of atrial action potentials. **METHODS AND RESULTS:** We took advantage of a mouse model with site-specific insertion of a tetracycline-based genetic switch in the 5' untranslated region of the KCNN3 (SK3 channel) gene (SK3(T/T)). The gene-targeted animals overexpress the SK3 channel without interfering with the normal profile of SK3 expression. Whole-cell, patch-clamp techniques show a significant shortening of the action potential duration mainly at 90% repolarization (APD90) in atrial myocytes from the homozygous SK3(T/T) animals. Conversely, treatment with dietary doxycycline results in a significant prolongation of APD90 in atrial myocytes from SK3(T/T) animals. We further demonstrate that the shortening of APDs in SK3 overexpression mice predisposes the animals to inducible atrial arrhythmias. **CONCLUSION:** SK3 channel contributes importantly towards atrial action potential repolarization. Our data suggest the important role of the SK3 isoform in atrial myocytes.

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